REMARKS

Claims 89-94 are pending in this application. Claims 1-88 have been previously canceled without prejudice or disclaimer. Applicants, by canceling any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein in a continuing application.

Presently pending independent claim 89 recites "a method for treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal therapeutically effective amounts of (i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and (ii) all trans retinoic acid." Claims 90 and 91 depend from claim 89.

Presently pending independent claim 92 recites "a treatment combination for acute myeloid leukemia (AML) comprising (i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and (ii) all trans retinoic acid." Claims 93 and 94 depend from claim 92.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. ***At pages 2-5 of the Official Action, claims 86-94 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gaspar Elsas et al., "Murine myeloid progenitor responses to GM-CSF and eosinophil precursor responses to IL-5 represent distinct targets for downmodulation by prostaglandin E_2," British Journal of Pharmacology, pp. 1362-1368, vol. 130 (2000), Reid, P., "Roflumilast," Current Opinion in Investigational Drugs, pp. 1165-1170, vol. 3, no. 8 (2002) and Sacchi et al., "All-Trans Retinoic Acid in Hematological Malignancies. An Update," Heaematologica, pp. 106-121, vol. 82 (1997) in light of Zhao et al., "Inhibitor binding to type 4 phosphodiesterase (PDE4) assessed using [^{3}H] Piclamilast and [^{3}H] Rolipram," The Journal of Pharmacology and Experimental Therapeutics, pp. 565-572, vol. 305, no. 2 (2003).***

In the Advisory Action, the Examiner asserts that the reply filed February 24, 2009, did not place this application in condition for allowance because Applicant's remarks were not persuasive. In particular, the Examiner asserts that it would have been obvious to modify the cited references to arrive at the presently claimed subject matter, while acknowledging that none of the cited references teach or suggest the use of roflumilast and ATRA, either alone or in combination, for the treatment of acute myeloid leukemia (AML), as presently claimed.

In view of the following, Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U. S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person

having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*.

Applicants respectfully note that claims 86-88 have been canceled without disclaimer or prejudice, thereby rendering their rejection moot.

Independent claim 89 is directed to a method for treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal therapeutically effective amounts of (i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide

(Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and (ii) all trans retinoic acid. Claims 90 and 91 depend from claim 89.

Independent claim 92 is directed to a treatment combination for AML comprising (i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoro-methoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and (ii) all trans retinoic acid. Claims 93 and 94 depend from claim 92.

In contrast, Gaspar Elsas et al. describe that a significant decrease in the total number of myeloid colonies formed by naive BP-2 bone-marrow cells in the presence of GM-CSF and Rolipram (10^{-5} M) was observed, relative to the control cultures with GM-CSF alone. *See* Gaspar Elsas et al. at page 1364, column 1, paragraph 2. Applicants respectfully note that Gaspar Elsas et al. describe that the PDE4 inhibitor Rolipram, as well as other compounds well known in the art to augment cAMP, such as PGE_2 or the cAMP analogue dibutyryl cAMP, inhibit GM-CSF induced colony formation (proliferation) of ***normal, i.e., healthy*** myeloid progenitor cells derived from murine bone marrow *in vitro.* *See* Gaspar Elsas et al. at page 1364, Table 1. But Gaspar Elsas et al. do not teach or suggest the use of myeloid ***leukemia*** cells. In particular, Gaspar Elsas et al. do not describe the use of ***diseased cells***, e.g. commonly used cell lines such as NB4 or blasts from AML patients. Accordingly, Gaspar Elsas et al. do not teach or suggest that PDE4 inhibitors may be useful for the treatment of AML.

Reid, Sacchi et al., and Zhao et al. do not remedy the deficiencies of Gaspar Elsas et al. Reid describe that Roflumilast is a potent PDE4 inhibitor with superior oral bioavailability than Piclamilast. *See* Reid at page 1168, column 2. However, Applicants respectfully submit that Reid does not describe the use of Roflumilast and ATRA, either alone or in combination, for the treatment of AML. Sacchi et al. describe that retinoids show some activity in the treatment of chronic myeloid leukemia (CML). *See* Sacchi et al. at the Abstract. However, Sacchi et al. does not describe the use of Roflumilast and ATRA, either alone or in combination, for the treatment of AML. Zhao et al. describe that Piclamilast is a more potent PDE4 inhibitor than Rolipram. *See* Zhao et al. at p. 566, paragraph 2. Zhao et al. do not describe the use of Roflumilast and ATRA, either alone or in combination, for the treatment of AML.

As such, none of Gaspar Elsas et al, Reid, Sacchi et al., and Zhao et al. describe a method for treating AML in a mammal, comprising administering to said mammal therapeutically effective amounts of a compound selected from the group Roflumilast, Roflumilast-N-Oxide and pharmaceutically acceptable salts thereof; and ATRA, as presently claimed. Further, Applicants submit that the skilled artisan would not have been motivated to arrive at the presently claimed subject matter, because none of Gaspar Elsas et al., Reid, Sacchi et al., and Zhao et al., either alone or in combination, teach or suggest the use of Roflumilast and ATRA for the treatment of AML, as presently claimed. Accordingly, Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because, whether taken alone or

together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*.

As such, the Examiner has failed to demonstrate a *prima facie* case of obviousness against pending claims 89-94. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based upon the remarks, the presently claimed subject matter is believed to be patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 89-94. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments. The Examiner is specifically authorized to charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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